Dermatology Practical & Conceptual

Long-Term Omalizumab Therapy in Patients with Chronic Spontaneous Urticaria: Does it Increase the Risk of COVID-19?

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ABSTRACT

Introduction: Based on the existing literature, omalizumab (OMZ) is considered a safe treatment modality in chronic spontaneous urticaria (CSU) during the coronavirus disease 19 (COVID-19) era.

Objectives: The aim of this study is to evaluate the effects of OMZ on CSU patients regarding COVID-19 infection.

Methods: In this retrospective study, files of CSU patients using OMZ during the COVID-19 pandemic were reviewed in terms of demographic features, medical history including COVID-19 vaccination status, clinical characteristics, pretreatment laboratory parameters, duration, and dosing regimen of OMZ treatment. Patients with a history of COVID-19 infection while on OMZ therapy and patients without COVID-19 history were compared with respect to these parameters. The urticaria activations following COVID-19 infection or vaccination were also recorded.

Results: Sixty-eight patients with CSU (female:male ratio = 1.8:1; mean age = 47.2 ± 15.1 years) continued to receive OMZ treatment. The median duration of OMZ treatment was 12 months (range: 6-60). Twelve patients (17.6%) were diagnosed with COVID-19 showing no exacerbation in urticaria. The duration of OMZ treatment was significantly higher in the group with COVID-19 infection history compared to patients with no history of COVID-19 (P = 0.01). Among 51 patients (75%) vaccinated against COVID-19, urticaria activation occurred in 4 patients without any recurrence following booster vaccinations.

Conclusions: Considering the likelihood of increased COVID-19 infection risk in the setting of long-term OMZ in CSU patients, the duration of OMZ therapy might be kept at a minimum, or a temporary interruption of the treatment period might be preferred, particularly in high-risk patients regarding COVID-19.

Introduction

Chronic spontaneous urticaria (CSU) is a disease lasting more than six weeks and characterized by recurrent erythematous, indurated lesions. Infections, drugs, and vaccines are possible triggers that may cause CSU exacerbations. The current CSU management guideline recommends non-sedative antihistamines in standard or up to 4-fold higher dosages as the first-line treatment. In refractory cases, the anti-immunoglobulin E (anti-IgE) antibody omalizumab (OMZ) is the therapy of choice [1,2].

Coronavirus disease 2019 (COVID-19) had significant impacts on general health practices. Several cases of urticaria triggered by COVID-19 or the vaccines developed against the virus have recently been reported [3-5].

CSU adversely affects the quality of life of the patients [1,2]. Moreover, patients with treatment-resistant CSU may be concerned about the reactivation of their disease. For this reason, they may refrain from the newly developed therapeutic options. At the beginning of the COVID-19 pandemic, many patients even considered discontinuing their regular medications due to possible immunosuppression. A similar situation was observed for OMZ treatment, which has no immunosuppressive effect.

Objectives

In this study, we aimed to investigate the effect of OMZ treatment on CSU patients regarding COVID-19 incidence and prognosis.

Methods

In this retrospective cohort study, CSU patients who were followed up in a tertiary referral center and used at least six months OMZ therapy between April 2020 and April 2022 were assessed. Patients under the age of 18 and those receiving OMZ treatment for less than six months were excluded.

The medical files of the patients were evaluated regarding demographic characteristics (gender, age), medical history (comorbidities, concomitant treatments including antihistamines, COVID-19 vaccination status), clinical features (presence of urticaria, angioedema or both, disease activity), laboratory findings (including pre-treatment Ig-E levels and blood eosinophil counts), OMZ treatment duration and dosing frequency. The disease activity was evaluated with urticaria activity score 7 (UAS7) [1,2]. The rate of COVID-19 infection in patients during OMZ therapy was recorded. Patients with a history of COVID-19 infection while on OMZ therapy and patients without COVID-19 history were compared with respect to the parameters mentioned above. Moreover, urticaria exacerbations following COVID-19 and COVID-19 vaccines were noted.

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables which were expressed as mean ± standard deviation (SD) or median (min-max) in the presence of abnormal distribution, and categorical variables were expressed as percentages. Comparisons between the groups were made by using chi-square or Fisher exact test for categorical variables, independent samples t-test for normally distributed continuous variables, and Mann-Whitney U test when the distribution was skewed. A P -value less than 0.05 was considered statistically significant. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc.).

The Ethics Committes of 18 Mart University approved the study with the decision number 2022/14-09.

Results

A total of 68 patients with CSU continued to receive OMZ treatment during the study period. The demographic and clinical characteristics of patients are summarized in Table 1. The female: male ratio was 1.8:1, while the mean age of the patients was 47.2 ± 15.1 years.

Urticaria was accompanied by angioedema in 25 patients (36.8%). The median IgE level measured prior to OMZ treatment was 281 kU/L (range: 2-2730). Pre-treatment eosinophilia was detected in six patients (9%).

The median duration of OMZ treatment was 12 months (range: 6-60). A standard dose regimen (300 mg every four weeks subcutaneously) was initiated for all patients, while two patients required a reduction in dosing intervals (300 mg every two weeks). An oral H1-antihistamine was required in addition to OMZ in 24 patients (35.3%) to maintain the disease control. The most commonly used H1-antihistamine was levocetirizine (N = 17, 70.8%).

Table 1. Demographic and clinical characteristics of the chronic spontaneous urticaria patients using omalizumab treatment.

Characteristics	
Number of patients, N (%)	68 (100%)
Gender, N (%)	
Female	44 (64.7)
Age (years), mean ±SD	47.2±15.1
Comorbidities	4 (5.8)
Hypothyroidism	2 (2.9)
Hypertension	1 (1.5)
Depression	1 (1.5)
Oral H1 antihistamine therapy, N (%)	24 (35.3)
Levocetirizine	17 (25)
Ebastine	2 (2.9)
Hydroxyzine	2 (2.9)
Bilastine	1 (1.59
Rupatadine	1 (1.5)
Fexofenadine	1 (1.5)
Vaccination status, N (%)	
No vaccination	10 (14.7)
Inactivated vaccine[a]	27 (39.7)
mRNA vaccine[b]	19 (27.9)
Inactivated vaccine[a]+mRNAvaccine[b]	12 (17.6)
Presence of angioedema, N (%)	25 (36.8)
Total IgE prior to OMZ treatment(kU/L), median (range)	281 (2-2730)
Presence of eosinophilia prior to OMZ treatment, n (%)	6 (9)
OMZ treatment duration (month), median (range)	12 (6-60)
Dosing regimen of OMZ, N (%)	
300 mg every 4 weeks	66 (97.1)
300 mg every 2 weeks	2 (2.9)

OMZ = omalizumab; SD = standard deviation.
[a]Inactivated vaccine produced by SinovacBiotech®.
[b]mRNA vaccine produced by Pfizer/BioNTech®.

Twelve of the 68 CSU patients (17.6%) receiving OMZ were diagnosed with COVID-19 during OMZ treatment. All twelve patients (17.6%) were diagnosed with COVID-19, confirmed by polymerase chain reaction (PCR) test. None of the other 56 patients had a history of COVID-19 before or during OMZ treatment. All patients had mild symptoms during the course of the disease and did not require hospitalization. Furthermore, no urticaria activation was observed in any patients following COVID-19. The UAS7 score was noted to be zero before and after COVID-19. When the patients with confirmed COVID-19 were compared with those who did not acquire the infection, no difference was detected regarding gender, age, comorbidities, COVID-19 vaccination status, pre-treatment Ig E levels, pre-treatment eosinophilia, and treatment regimens utilized for CSU. In four of 12 patients, the total IgE level prior to OMZ treatment was below 110 kU/L. On the other hand, the duration of OMZ treatment was significantly higher in the group with COVID-19 infection history (P = 0.01) (Table 2).

Fifty-one (75%) patients had been vaccinated against COVID-19 while using OMZ. Urticaria activation following vaccination occurred in four patients: one patient who had received inactivated vaccine (Sinovac®) and three patients who had received the mRNA vaccine (BioNTech®). Activation developed in all patients after the first dose of vaccination and within an average of two days. The urticaria symptoms subsided rapidly in all patients with the administration of oral antihistamine treatment (levocetirizine BID). No recurrence was observed following booster vaccinations in any of the patients.

Conclusions

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has direct and indirect impacts on the immune system.

Table 2. Comparison of demographic and clinical characteristics of patients according to Covid-19 infection history.

	COVID-19 (+) N=12 (17.6%)	COVID-19 (-) N=56 (82.4%)	P
Gender, N (%)			
Female	10 (83.3)	34 (60.7)	0.190
Age (years), mean ±SD	39.6±12.8	48.8±15.1	0.056
[c]Comorbidity, N (%)	1 (8.3)	3(5.4)	0.549
Oral H1-antihistamine therapy, N (%)	4 (33.3)	20 (35.7)	1
Vaccination status, N (%)			0.699
No vaccination	2 (16.7)	8 (14.3)	
Inactivated vaccine[a]	3 (25)	24 (42.9)	
mRNA vaccine[b]	4 (33.3)	15 (26.8)	
Inactivated vaccine[a]+mRNA vaccine[b]	3 (25)	9 (16.1)	
Presence of angioedema, N (%)	6 (50)	19 (33.9)	0.335
Total IgE prior to OMZ treatment (kU/L), median (range)	312.5 (31-740)	280 (2-2730)	0.876
Presence of eosinophilia prior to OMZ treatment, N (%)	2 (16.7)	4 (7.7)	0.291
OMZ treatment duration (months), median (range)	22.5 (10-60)	12 (6-60)	0.01
Dosing regimen of OMZ, N (%)			1
300 mg every 4 weeks	12 (100)	54 (96.4)	
300 mg every 2 weeks	0 (0)	2 (3.6)	

OMZ = omalizumab; SD = standard deviation.
[a]Inactivated vaccine produced by SinovacBiotech®.
[b]mRNA vaccine produced by Pfizer/BioNTech®.
[c]In the COVID-19 + group, one patient had hypertension, while in the COVID-19 -group, two patients had hypothyroidism and one patient had depression.

The virus is considered to cause a three-phase disease. The initial phase begins with the entry of the virus into the host and lasts about 5-7 days. The second phase, namely the pulmonary phase, is characterized by pulmonary involvement and occurs within 7-15 days following the disease onset. In the third phase, the inflammatory phase, overactivation of the immune system leads to cytokine storm and consequent development of acute respiratory distress syndrome (ARDS) [6]. An adequate immune response during the initial phase is desirable, while the primary goal of the treatment is the prevention of the over-activation encountered during the following two phases resulting in cytokine storm [7].

OMZ is a recombinant human IgE antibody that exerts its effect by preventing the binding of IgE with high-affinity IgE receptors (FcεRI). It is utilized in disorders in which IgE plays a major role in pathogenesis, such as CSU and asthma. Furthermore, the antiviral effect of OMZ has been reported in various studies. This antiviral effect occurs in several different ways. There is a considerable number of FcεRIs on the surface of plasmacytoid dendritic cells (pDCs) responsible for IFN- α production. In several studies, it has been suggested that elevated serum IgE levels and increased pDC FcεRI expression might reduce IFN- α secretion from pDCs. Thus, OMZ contributes to the release of IFN-α by reducing the level of IgE and FcεRIs [8-10]. Moreover, OMZ has been demonstrated to improve nasal sinus function, which has a significant role in the first line of defense against SARS-CoV-2 [11,12]. Hence, patients using OMZ might benefit from the treatment during the initial phase of COVID-19, and some studies highlighted that OMZ might be a preferable treatment option for COVID-19 [12,13].

OMZ also lessens the disease severity by reducing FcεRIs on the surface of mast cells, which play a key role in the inflammatory response during the second and third phases of COVID-19 and the prolonged COVID-19 symptoms referred to as "long-COVID" [12-14].

In our study, among 68 patients using OMZ during the COVID-19 pandemic, twelve contracted the SARS-CoV-2 infection. All patients recovered without progressing to the second pulmonary phase. Apart from these twelve patients whose diagnoses were established with a positive PCR test, there might be asymptomatic and underdiagnosed patients.

The duration of OMZ treatment was significantly longer in the patient group with a history of COVID-19 compared to patients who did not acquire the infection in our series, although there was no difference between the two groups in terms of COVID-19 vaccination status. This might

be attributed to a paucity in immune response in the initial COVID-19 phase in patients on long-term OMZ therapy. SARS-CoV-2 enters the host cells through binding the angiotensin-converting enzyme 2 (ACE2) via S-protein [15]. ACE2 receptor possesses a significant role in the initiation of COVID-19 since SARS-CoV-2 can only enter cells with ACE2 receptors. Zietkowski et al demonstrated lowered endothelin-1 (ET-1) levels in patients receiving OMZ. The authors reported that the reduction was more pronounced in patients with more extended treatment duration [16]. In another study, a negative correlation was revealed between ET-1 and ACE2 receptor, ie, the number of ACE2 receptors was elevated as the ET-1 level declined [17]. In addition, patients with higher ACE2 receptor levels were shown to have a better COVID-19 prognosis [18]. It might be a possible explanation for the higher incidence of COVID-19 in our patients with a longer duration of OMZ therapy and the low disease activity that did not necessitate hospitalization in any of these patients.

In the aforementioned study, Zietkowski et al observed a reduction in the eosinophilic cationic protein (ECP) levels and the blood eosinophil counts in subjects on OMZ therapy in proportion to the treatment duration [16]. Studies investigating the relation between COVID-19 and eosinophil levels indicated eosinopenia, particularly in the initial disease phase [19,20]. On the other hand, COVID-19 incidence was relatively low in patients with asthma, a disease associated with elevated eosinophil count, suggesting eosinophilia might be a protective factor against COVID-19 [21-22]. In the light of these findings, it might be speculated that the extended use of OMZ facilitated the entry of SARS-CoV-2 in the host cell by increasing the ACE2 receptors and reducing eosinophil counts, while hindering the progression of the disease into more severe forms with its antiviral and anti-inflammatory effects.

Various case reports and studies confirmed urticaria activation triggered either with COVID-19 or COVID-19 vaccines [23-25]. In contrast, none of the patients in our series who had COVID-19 showed activation of urticaria. Similarly, some studies observed no urticaria activation in patients on OMZ in the setting of COVID-19 [13,25]. On the other hand, the urticaria flares following vaccination were not uncommon and were mainly detected following mRNA vaccines as in our patients [24].

In conclusion, our study highlights the positive relationship between the duration of OMZ treatment and the risk of acquiring SARS-CoV-2. Older age (≥65 years old), male gender, hypertension, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, and malignancies were associated with a higher risk of death from COVID-19 infection [26]. In this regard, in patients with aforementioned risk factors, the physicians might consider a temporary interruption of OMZ therapy following control of CSU symptoms to allow ET-1 and eosinophil levels to return to levels before OMZ administration.

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